

BRIEF ON APPEAL
Serial Number: 09/606,137
Filing Date: June 28, 2000
Title: IMAGING METHOD FOR VISUALIZING IMPLANTED LIVING CELLS

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Docket No.: 500.003US1



S/N 09/606,137

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: MICHEAL E. MOSELEY et al.

Examiner: JUNG, William

Serial No.: 09/606,137

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Filing Date: 28 JUNE 2000

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MAIL STOP: APPEAL BRIEF - PATENTS

P.O. BOX 1450

Commissioner for Patents

Alexandria, VA22313-1450

Sir:

The U.S. Patent and Trademark Office is hereby authorized to debit any costs and fees associated with this Petition to Deposit Account No. 50-1391. Applicants request a personal appearance at a hearing before the Board of Appeals and Patent Interferences, the fees for that hearing being postponed until after receipt of the Examiner's Answer.

CERTIFICATE UNDER 37 C.F.R. 1.8: The undersigned hereby certifies that this Transmittal Letter and the paper, as described herein, are being deposited in the United States Postal Service, as first class mail, with sufficient postage, in an envelope addressed to: MAIL STOP: APPEAL BRIEF - PATENTS, P.O. BOX 1450, Commissioner for Patents, Alexandria, VA 22313-1450 27 January 2006.

Mark A. Litman
Name

Signature

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REAL PARTY IN INTEREST

The real party in interest in this Appeal is the assignee of the full right, title and interest in this Application, The Regents of the University of Minnesota in Minneapolis, Minnesota and Stanford University in Palo Alto, California. The exclusive licensee of this Application is NexGen, Inc, a small entity corporation having a place of business at 3930 Pomo Place, Davis CA 95616.

RELATED APPEALS AND INTERFERENCES

The Appellant(s), the legal representative prosecuting this application and Appeal, and the assignee are not aware of any Appeals or Interferences that will directly affect or have a bearing on the Board's of Patent Appeals and Interferences decision in this pending Appeal.

STATUS OF CLAIMS

Claims 5-7, 9, 11-26, 29 and 54-64 are all of the claims remaining in this application, all other claims having been voluntarily cancelled during prosecution of this application, Applicants reserving the rights to file continuation application son the subject matter of those cancelled claims and other subject disclosed but not claimed in this Application.

Claims 5-7, 9, 11-26, 29 and 54-64 have been finally rejected under 35 USC 103(a) with various combinations of references cited against the claims. Specifically:

- 1) Claims 5-7, 9, 11-19, 23, 25, 26, 29 and 64 (believed to be intended to read 54-64, although misstated on the Office action at page 2) have been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) and Palti (US Patent No. 5,190,041);
- 2) Claims 20-22 have been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) and Palti (US Patent No. 5,190,041), when further considered with Johnson et al. (US 6,505,208).
- 3) Claim 24 have been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) and Palti (US Patent No. 5,190,041), when further considered with Dinsmore (US 6,140,116).

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STATUS OF AMENDMENTS

An amendment filed under 37 C.F.R. 1.111 on July 29, 2005 (Certified Mailing date of July 27, 2005) has been entered without objection. No amendment after final rejection was submitted.

SUMMARY OF CLAIMED SUBJECT MATTER

Metabolically viable cell implants can be distinguished from dead or dying cells based on quantitative regional indications of changes in signals resulting from the metabolic activity (or change in activity) of implanted cells, the inactivity of implanted cells, quantitative indications of increased (or decreased) cell chemical product due to increased (or decreased) numbers of active cells, and/or quantitative changes in lactate to metabolite levels. In another embodiment, a quantitative assessment of the populations of living to dead cells is obtained from the molar ratios of the proton signals that can be quantitated to resulting changes in local chemistry environments, as from changes due from concentration changes from converting lactate to metabolites. (Page 6, lines 9-17 of original specification as filed)

A wide range of chemical and physical properties in the environment of implanted cells are monitored to sense a property within the region of a patient that is indicative of quantitative change in cell viability or nonviability of transplanted progenitor or stem cells grown in a culture. Using data from sensing the property within the region provides a quantitative indication of cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein the cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population. (Original claims 1 and 5)

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

Solely for the purposes of expediting this Appeal and complying with the requirements of 37 C.F.R. 1.192(c)(7), groups claims in the Arguments of Appellants. This grouping is not intended to constitute any admission on the record that claims within groups may or may not be independently asserted in subsequent litigation or that for any judicial determination other than this Appeal, the claims may or may not stand by themselves against any challenge to their validity or enforceability. The generic grounds of rejection are:

- a) Claims 5-7, 9, 11-19, 23, 25, 26, 29 and 64 (believed to be intended to read 54-64, although misstated on the Office action at page 2) have been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) and Palti (US Patent No. 5,190,041);
- b) Claims 20-22 have been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) and Palti (US Patent No. 5,190,041), when further considered with Johnson et al. (US 6,051,208).
- c) Claim 24 have been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) and Palti (US Patent No. 5,190,041), when further considered with Dinsmore (US 6,140,116).

ARGUMENT

Claims 5-7, 9, 11-26 and 29 have been rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041)

Claim 5 will first be discussed to emphasize specific limitations (not to the exclusion of other limitations or claim) that are particularly material to differentiation from this combination of references. Claim 5 recites:

A method for indicating viability of transplanted progenitor or stem

cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and

using data from sensing said property within said region **to indicate cell viability** from a transplant of progenitor or stem cells grown in a culture within the region **wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.** (Emphasis added).

Specific Errors in the Asserted factual Content of the Basic Reference, Lemelson

It is asserted that in Column 1, line 16 through column 2, line 16; column 3, line 28 through column 4, line 45; and column 10, lines 22-55 of the Office Action that Lemelson teaches “monitoring the viability of the tissue condition in response to the growth factor. This is not seen to be the actual content of the Lemelson disclosure. As

noted from a complete quotation of this disclosure from Lemelson (provided below), the disclosure actually describes the use of imaging to guide the delivery of cells and materials expected to produce beneficial results on the cells. **There is no monitoring of sensing properties of cell responses as recited in the claims, especially no sensing of such cell responses as chemical responses as recited in some of these claims.** The Lemelson disclosure is presented below, the highlighted portions emphasizing that Lemelson does not disclose the recited format of monitoring cell response. **ON THIS SINGLE ISSUE, although other issues will be noted, THE REJECTION IS CLEARLY IN ERROR AND MUST FAIL.**

Column 1, line 16 – column 2, line 16 (Lemelson)

In accordance with the invention, a computer controlled injection needle is employed to inject a therapeutic agent into select target tissue of a patient, for example, a tumor. The tumor is located using one or more scanning modalities capable of distinguishing the target tissue such as plain view X-ray, computerized axial tomography X-ray (CAT scanning), magnetic resonance imaging (MRI scanning), positron emission tomography (PET scanning), and ultrasound scanning. Once the target tissue is located and its borders defined by the imaging modality, location coordinates are generated and assigned with respect to a support structure supporting the patient. A manipulator arm assembly under computer control is used to move and operate the injection needle. **A stored program, having user defined parameters and the location coordinate data, then directs the injection needle to a plurality of sites on the patient's body at corresponding insertion depths which result in positioning the tip of the injection needle into the target tissue at various locations. The therapeutic agent is then injected in controlled amounts at each such injection location.** In this manner, the agent may be delivered to the target tissue with greater precision than with prior methods so that less of the therapeutic agent is delivered to non-target tissue where its effects may be deleterious.

The present invention may also be employed with therapeutic agents for effecting tissue engineering, that is the selective growth of various cell types within a target tissue of a patient. One such embodiment uses an agent comprising a growth factor or cytokine in conjunction with another agent for creating specificity. A growth factor may then be employed to cause the selective growth of specific living tissue via cellular proliferation without causing the undesired

proliferation of other cell types normally responsive to the growth factor. Growth factors which can be used with such method include those of broad specificity such as EGF, PDGF, fibroblast growth factors (FGFs), hepatocyte growth factor (HGF), insulin, insulinlike growth factor (IGF-1), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and macrophage colony stimulating factor (M-CSF). Such method may be useful not only in treating certain disease states where specific cellular proliferation is of value, but also in enhancing the production of animal products such as milk from dairy cattle and various hormones from genetically engineered animals.

In order to produce such a selective growth agent, a specific growth factor or other cytokine is selected which elicits a desired response (eg., cellular proliferation) in a specific target cell of a multicellular organism. Monoclonal antibodies are then produced which have a specific binding affinity for other cells of the organism that also respond to the growth factor, which other cells are referred to herein as non-target cells. Such monoclonal antibodies are directed toward antigenic determinants that are expressed by non-target cells but not by target cells. The monoclonal antibodies are then conjugated with a protein corresponding to the extracellular domain of the growth factor receptor. In order to eliminate the response of the non-target cells to the growth factor, the monoclonal antibody conjugate is administered together with the growth factor by employing the computer controlled injection needle apparatus as described above. The antibody conjugate then binds to the non-target cells and presents a binding site for the growth factor that results in competitive inhibition of the growth factor's binding to the cell's native growth factor receptor. The target cells, on the other hand, are left fully responsive to the growth factor. The method may also be combined with other techniques for causing tissue growth such as electrical stimulation, used presently for promoting bone healing, as well as specific nutrients needed for cell growth.

As can be readily seen, there is **ABSOLUTELY NO DISCLOSURE OF MONITORING CELL RESPONSE AS RECITED IN THE CLAIMS AS ASSERTED IN THE REJECTION.**

Column 3, line 28 through column 4, line 45 (Lemelson)

The location coordinates of select tissue of a living being into which select tissue a therapeutic agent (such as a drug, genetic material, a selective growth factor composition, or a transplant medium containing cellular transplants) **is to be injected are defined or computed with respect to images of the patient's anatomy** defining anatomical structures which may be generated, for

example, by employing computerized axial tomography (CAT scanning), magnetic resonance imaging (MRI), ultrasonography, PET, infrared or microwave imaging, or other types of electronic scanning. In accordance with the present invention, a computer image of a select anatomical area is generated by using one or more of such conventional imaging modalities. A location coordinate with respect to a patient support structure is assigned to each pixel making up the image. **The anatomical region into which it is desired to deliver the therapeutic agent is then located on the electronically generated image or images by a radiologist**, for example, with selected of the pixels making up the image of the region serving to define the transplant location. A preferred means by which this can be performed is to display the images on a display monitor having a manually positionable cursor for outlining an area containing the lesion. The operator of the system then inputs to a computer digital data in the form of codes defining the anatomical location to which a cellular transplant or transplants are to be delivered as represented by the select pixels within the outlined area. As described below, each pixel of the body or organ image displayed by the computer has assigned to it a set of location coordinates calculated or defined with respect to a structure, such as a table supporting the patient, while the imaging is performed. The same or a similar patient support structure is then utilized during the injection procedure, **the injector or injection needle is carried in movement by the manipulator or catheter under computer control, inserted into select tissue, and operated so as to deliver the agent to select location coordinates with respect to the support structure**. In a typical embodiment, a first computer program calculates the location coordinates of select body regions as defined by pixels of images produced by **an imaging device using coded signals representing the sensed relative positions of the patient support in the imaging device, while a second computer program calculates the location coordinates of the injection needle and determines when the needle is located in the select body region into which it is desired to deliver the therapeutic agent**.

In one form, the patient is required to be in the same position with respect to the support structure during both the imaging and injection procedures so that the location coordinates selected will correspond to the proper anatomical region of the patient. One way of accomplishing this is to use a patient support structure having a moldable support structure defining a surface that can be made to conform to the shape of the patient's body as a kind of body cast. Once such a body impression is made, the patient may be placed in substantially the same position on the support structure for both scanning/imaging and subsequent transplantation procedures. Such a moldable patient support may also serve to

immobilize the patient during both procedures. Other patient restraint devices, such as straps and adjustably positionable table stops, may also be employed.

The manner of assigning location coordinates to each image pixel depends upon the particular imaging modality. For example, with a conventional CAT scanner, the x-ray tube emits a narrow beam of x-rays toward the patient with an x-ray detector, such as an array of scintillation detectors, positioned on the opposite side of the patient on which an x-ray shadow is formed. The x-ray tube and detectors, mounted on a rigid gantry, are rotated in multiple steps about the body until an entire axial slice is viewed from multiple angles. Codes defining the data acquired by the scintillation detectors are entered into a computer which uses mathematical algorithms operable to reconstruct a cross-sectional image of the region examined. Such a computerized scanning arrangement calculates the degree to which the tissue interposed between the x-ray tube and the detectors absorb the x-ray beam and thereby provides an attenuation coefficient for each area of tissue examined. Essentially, the quantity of x-rays absorbed in small volumes(voxels) of body tissue in the slice is computed. Computer analysis of the data collected then allows assignment of a numerical value to each small area (pixel) of the cross-sectional plane. By means of a digital-to-analog converter, the numerical value of each pixel is translated to a gray scale value for driving a CRT display or the like.

Again, as can be readily seen, there is **ABSOLUTELY NO DISCLOSURE OF MONITORING CELL RESPONSE AS RECITED IN THE CLAIMS.**

Column 10, lines 22-55 (Lemelson)

In the replication of unicellular organisms, where each cell division generates a new individual, proliferation is controlled by the type and supply of nutrients in the medium in which the organisms reside. In the growth and replication of multicellular organisms, on the other hand, the component cells thereof must obey strict control parameters that limit their proliferation in order to produce and maintain the intricate organization of the multicellular body. At any point in time, most of the cells in a multicellular organism may be in a resting, non-proliferative state even though the supply of nutrients are plentiful. The cells of a multicellular organism are intrinsically unable to divide unless they are provided with positive signals from other cells. Many of these positive signals are in the form of cytokines and growth factors which bind to complementary receptors in the plasma membrane of responsive cells to stimulate cell

proliferation via a signal transduction pathway. In this way, the negative controls that otherwise restrain growth are overridden.

Most cytokines and growth factors are proteins, although non-protein growth factors also exist, such as steroid hormones which act on intracellular receptor proteins. As of the date of this application, over fifty such protein growth factors have been discovered, and they can be divided into broad and narrow specificity classes. Factors with broad specificity, such as platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), affect many classes of cells. Thus PDGF acts on a number of target cells including fibroblasts, smooth muscle cells, and neuroglial cells. EGF, while acting mainly on epidermal cells, also acts on many other cell types. At the other extreme are narrow specificity growth factors such as erythropoietin whose sole action is to induce proliferation of red blood cell precursors.

This section of Lemelson deals only with background information on the nature of growth factors. Again, as can be readily seen, there is **ABSOLUTELY NO DISCLOSURE OF MONITORING CELL RESPONSE AS RECITED IN THE CLAIMS.**

At an absolute minimum, the rejection fails from the fact that there is absolutely no teaching in Lemelson (**as asserted**) that there is monitoring of the viability of implanted cells. As that teaching is absent, all rejections based on the assertion of this teaching in Lemelson are in error and must be withdrawn. **As this assertion is a fundamental part of every rejection in the Final Office Action, and is material to every claim that has been rejected, this failure renders every rejection reversible and in error.**

A more detailed analysis of Lemelson is also provided here. The Lemelson U.S. Patent No. 5,865,744 reference cited by the examiner (which was also cited as prior art in this patent application) discloses methods for using MRI and other imaging technologies to deliver drugs and cellular transplants to a patient under the control of a computer. **Lemelson does not disclose delivery of progenitor or stem cells as recited, and most importantly does not quantitatively monitor the cells for viability as recited in the claims.** Nonetheless, the examiner asserts that "Lemelson's use of growth factor

materials and cells as transplant agents to proliferate cell or tissue growth is equivalent to the intended purpose of the claimed invention in current application”. Again, in the Lemelson reference, there is no quantitative monitoring of the cell response to the introduction of these materials.

Furthermore, and contrary to the examiner’s assertion, image-guided delivery of progenitor and stem cells imposes delivery and monitoring requirements that are not covered or anticipated by Lemelson’s patent. For example, since embryonic stem cells are in an early and undifferentiated stage of development, they are more susceptible than other cells to environmental and physiological factors, including trophic factors at the site of cell placement and the techniques used for cell delivery. It is generally known that conventional catheter-based techniques for intracerebral delivery of cells, such as those disclosed by Lemelson, can provoke inflammatory tissue reactions, hemorrhage, necrosis, and degeneration and are therefore not suitable for delivering stem cells. Traumatic changes at the implant site can compromise cell survival or disrupt the ability of the implanted embryonic stem cell implant to form viable functional nerve connections with existing neurons in the brain. According to the novel teachings of Appellants in this Application, following image-guided delivery of progenitor and stem cells using specialized catheters, cytoarchitectural changes can be monitored with high-resolution MRI methods, such as anisotropic diffusion coefficient mapping and diffusion tensor imaging. The MRI methods disclosed by the Appelants are particularly useful for non-invasively localizing the placement of the progenitor and stem cells, quantitatively assessing the number of surviving cells, and thereafter evaluating the functional integration of surviving transplanted cells with surrounding nerve tissues in the brain. These claimed technologies are disclosed by the Applicants, but are not taught by Lemelson.

Although Lemelson describes the use of MRI and CT to initially position the “therapeutic material” at target locations in tissues, he does not provide any method or

device that enables the monitoring of the distribution of injected drugs or the migration of implanted cells over time. It is well established in the medical literature that stem cells have a propensity to migrate from the site of implant to remote locations. It is also known that stem cell migration is influenced by trophic factors and pathophysiologic changes, such as ischemia. Thus, it is important that the present application provides an imaging method that can monitor cell migration and eventual in situ localization of implanted stem cells. Monitoring of cell migration and by MRI is not currently possible without the use of techniques such as catheter-based RF microcoil imaging or the use of cells labeled with an MR-visible label, which are disclosed in the present application (claims 13-16) but which are not taught by Lemelson.

The presently claimed technology may be further distinguished from the teachings provided by Lemelson on the basis that certain claims expressly provide for a quantitative assessment of various parameters related to cell viability, as follows:

- an imaging means for quantitating the number of cells implanted into a tissue in a human body.
- an imaging means for quantitating the number of living cells implanted into a tissue in a human body.
- an MR imaging means for quantitating the number of cell-to-cell membrane contacts in a cell implant in a tissue in a human body.
- an MR imaging method for quantitatively determining the apparent diffusion coefficient in a population of living cells implanted into a tissue in a human body.
- an MR method for quantitatively determining the pH and fluid-electrolyte parameters in a population of living cells implanted into a tissue in a human body.

- an MR method for quantitatively determining the phosphorus and water proton metabolites in a population of living cells implanted into a tissue in a human body.
- an MR imaging means for quantitating the functional capillary density of the tissue region contiguous with the cell implant.

Although the Lemelson reference describes a method “to predetermine the quantity and rate of flow of transplant medium or medication pumped to the injector,” neither Lemelson nor Palti discloses an imaging means for quantitatively assessing physiologic and metabolic parameters of progenitor or stem cell implants that can non-invasively determine cell viability. These teachings of Lemelson relate to prospective planning of surgical/interventional operations, as opposed to the claimed technology of a unique methodology of monitoring current operational events and past operational results. Lemelson is thus looking at a different time frame than Appellants’ claimed technology and is performing different tasks.

The Examiner admits that "Lemelson does not disclose indicating viability by determining from a group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function and dysfunction, volumetric expansion of cell population and volumetric decrease of cell population." It is now well established that poor implant survival is a key limitation to establishing transplant efficacy. Recent studies report that 80-95% of embryonic stem cells die within 48 hours after implantation. Moreover, surviving implanted cells may re-innervate only 25% of the host brain tissue and only at 25% of normal density. Published studies of embryonic stem cell implants have shown a 10- to 100-fold variability in cell survival and in graft volume. Pathophysiologic changes at the implant site that compromise cell survival, such as reduced blood flow, increased tissue pH, and abnormal tissue concentrations of ions and neurotransmitters can be monitored using the MR imaging and spectroscopy methods disclosed by the

applicants, but which are not even addressed in the Lemelson patent. Real time MR imaging at higher Tesla fields, such as disclosed by the applicants, can provide images identifying concentration changes of these introduced and production-stimulated materials, particularly by using RF microcoils in the region where the therapeutic agents are delivered.

The presently claimed technology in this application in particular discloses methods to monitor non-invasively the ongoing viability of the cell implant in terms of whether the cells are adequately perfused by the local microvasculature. In a further claiming of technology wholly distinct and unknown within the teachings of Lemelson, the present invention also discloses (and in some claims recites) a method for quantitating the functional capillary density in the anatomic region of the cell implant, for quantitatively determining the metabolic status of a population of living cells implanted into a tissue, and for the MR-assisted visualization of molecular level changes in composition of the cell implant.

Lemelson does not provide any quantitative method for monitoring the physiologic and metabolic status of the cell implant. The present invention, by comparison, provides an MR imaging method for controlled quantitative delivery (i.e., actual number of cells) into tissues of living cells and cell suspensions. The invention additionally discloses an imaging system to monitor the metabolic status of the transplanted cells and their assimilation into their tissue transplant environment based on quantitative MR indicators of cell growth and proliferation. The present invention provides a method by which metabolic changes arising from cell replication or cell death can be quantitatively measured using localized proton lactate and metabolite signals, and the resulting MR data provide a non-invasive quantitative assessment of cell viability.

The Use of the Palti Reference to Overcome the Deficiencies of Lemelson

Palti is cited as disclosing the fact that “implanted cells are detectable by imaging method to determine concentration over a period of time, which in turn determines the growth characteristics, increasing or decreasing which is due to cell death or proliferation (Col. Col. 2, line 63- col. 4, line 43; col. 4, line 65 – col. 5, line 13.” Because of the length of the first citation, only portions thereof will be completely analyzed below and the Examiner had been invited to point out any descriptions therein which are felt to be more relevant, but did not do so.

First it is to be noted with Palti, that the function of the invention is to monitor blood glucose levels, not primarily cell viability. Additionally and critically, Palti **IMPLANTS** electrodes into the region to measure electrical signals indicative of the secondary performance of glucose responsive cells that are not the primary transfer cells. The method of Palti is therefore not a direct measure of events indicative of implanted cell viability, is not an imaging method and is an invasive technique. In various claims, each of these required functions is excluded.

Claim 5 of the present application requires an indication of “wherein said cell viability is indicated by a property in cell chemistry” of the implanted progenitor or stem cells themselves. Palti, on the other hand, teaches the use of implanting glucose-sensitive cells into a tissue in order to provide an in vivo electrophysiological monitor of glucose levels in the medium surrounding the implanted glucose sensitive cells. Thus, Palti teaches only that exogenous implanted cells can be used as a surrogate biological marker of endogenous glucose levels. Palti’s secondary implanted cells measure only glucose activity which may then be used to adjust the patient’s insulin levels or to perform other interventions required to restore the patient to glucose balance. Palti’s data acquisition does not relate to implanted cell chemistry, implanted cell survivability and, in particular it does not relate to “...cell viability...indicated by a property in

cell chemistry...” . (See the Abstract, first sentence, Field of the Invention and the quoted portion from the Detailed Description of the Invention:

The present invention relates to means for monitoring the level of glucose in blood and bodily tissues Particularly, the invention relates to **a system for monitoring glucose with glucose sensitive cells that produce an electrical response to glucose levels in their surrounding medium** which is then used to determine the blood glucose level, to administer insulin or to take other measures to alter the blood glucose level such as diet adjustment.

Column 4, line 65 through Column 5, line 13 (Palti)

FIG. 1 schematically describes one embodiment of a system of the present invention which is described in further detail below. As shown at the upper right of FIG. 1, glucose diffuses from the bloodstream into the extracellular space in bodily tissues. Eventually the glucose diffuses to implanted glucose sensitive cells which are a part of the system of the present invention. The implanted cells respond by exhibiting electrical activity, such as a change in membrane potential, commensurate with the concentration of glucose in the extracellular space.

The electrical activity can be detected or monitored in one of two ways. Where the electrical activity is strong enough to be detected through a body surface (e.g., layers of skin), the electrical activity is detected directly by an external signal sensor. Alternatively, the electrical activity is monitored by an implanted signal pickup device. The pickup device processes and amplifies the electrical activity. The amplified signal is then transmitted through a body surface (such as the skin) and is detected by the external signal sensor.

This section describes monitoring glucose functions, not cell viability.

Col. 2, line 63- col. 4, line 43

In accordance with the present invention, systems are disclosed which utilize implanted glucose sensitive living cells to monitor blood glucose levels by monitoring glucose levels in bodily tissues in which the glucose level is in equilibrium with that of the blood. In this respect, the implanted cells are similarly situated to endogenous insulin secreting glucose sensitive cells. The implanted cells produce a detectable electrical or optical signal in response to changes in glucose concentration in surrounding tissue **The signal is then detected and interpreted to give a reading indicative of blood glucose levels. This reading can then be used as a basis for altering insulin or other drug dosage for injection,** as a basis for giving instructions to an external implanted insulin pump

to alter the amount of insulin delivered by the pump, or as a basis for taking other corrective measures, such as altering diet. As a result, blood sugar levels can be more closely monitored and controlled in a noninvasive way and insulin dosage can be more closely tailored with concomitant control of symptoms associated with diabetes.

A system for monitoring tissue and blood glucose level is disclosed which comprises glucose sensitive cells which are capable of producing a signal in response to changes in glucose concentration in the medium surrounding the cells. The signal produced can either be electrical or optical. In certain embodiments, the cells are contained in a capsule which is constructed from a membrane or similar substance which is impermeable to antibodies, yet permeable to nutrients to keep the cells alive. The capsule can also be fitted with means for collecting the signals produced by the cells.

More importantly, what is observed from this reading is that the signals produced by the implanted glucose monitoring cells are intended to reflect glucose homeostasis in the ambient tissues. The signals obtained from the surrogate glucoreceptors in the Palti invention are not intended to reflect cell viability of the implanted cells “wherein said cell viability is indicated by a property in cell chemistry.”

In instances where the signal is electrical, these collecting means can be metal electrodes which are placed in contact with the cells such that the signal produced by the cells can be measured as a potential difference between the electrodes. The system can further include an implanted signal pickup device which is connected to the electrodes in the capsule for processing (e.g., amplifying and modulating) the signal for later transmission through the body surface, such as the skin, or for transmission to an external or implanted insulin pump. Once the signal is processed the pickup device passes the signal on to means for transmitting the processed signal. In other embodiments, the implanted cells produce an electrical signal which can be detected by external electrodes without employing electrodes in the capsule or an implantable signal pick-up device.

In instances where the signal is optical, the signal is produced by a change in the optical qualities of the cells or specifically the membranes of the implanted cells. Preferably, the signal is produced by dyes contained within or coated on cellular membranes which will change the optical properties of the cells in response to changes in electrical activity of the cell. This change in optical quality can be

detected through relatively transparent body surfaces, such as thin skin layers or fingernails. Alternatively, the optical change can be measured by an implanted optical detector which processes the detected signal much as the implanted pick-up device previously described processes electrical signals. The processed signal can be used to control an insulin pump or transmitted through the skin for external detection.

The electrical signal or the optical signal are detected through the skin by an external sensor and then correlated to a corresponding blood glucose level. The sensor includes means for detecting the signal, means for processing such signal and correlating it to the corresponding blood glucose level, and output means for reporting or relating the blood glucose level as determined.

Alternatively, the implanted signal pickup device can pass a processed signal on to an implanted insulin pump, which, in response to such signal, delivers an appropriate dosage of insulin corresponding to the determined blood glucose level.

Capsules for use in practicing the present invention are also disclosed which comprise a membrane which is impermeable to antibodies and is permeable to nutrients necessary for cell growth. Glucose sensitive cells are enclosed within the membrane, along with electrodes in contact with the cells such that changes in the electrical activity of the cells can be detected as a potential difference between the electrodes.

Alternatively, in place of the electrodes, the capsules can enclose means for "shorting-out" the interior of the capsule with respect to the exterior of the capsule such that the electrical activity of the cells is optimally dissipated on the exterior of the capsule. As a result, the electrical activity will be maintained at a level which can be detected by appropriate sensing means.

Capsules are also disclosed which contain glucose sensitive cells which have been treated such that the cellular membranes of the cells are coated with dyes which are sensitive to change in cellular membrane potential.

Finally, methods of monitoring the blood glucose level employing the capsules and systems of the present invention are disclosed. Basically, those methods comprise implanting into the patient glucose sensitive cells, detecting the signal produced by the cells in response to levels and/or changes in glucose concentration and correlating that signal with the corresponding blood glucose level. Methods of administering glucose are also disclosed which comprise administering a level of insulin (or other correcting agent) appropriate to the blood glucose level determined in accordance with the methods disclosed herein. Such insulin can be either administered manually or by operation of an external or

implanted insulin pump which is connected to the detecting and monitoring system. It is understood that other therapeutic agents which will alter blood glucose levels, such as those sold under the tradenames "Dia Beta" (glyburide; Hoechst -Roussel), "Glucontrol" (glipizide; Pfizer) and "Diabinese" (chlorpropamide; Pfizer), can be substituted for insulin as described herein.

The Rejection apparently makes at least two assumptions from the teachings of Palti. First, Palti gives no teaching, instruction or suggestion that cell viability of the implanted cells themselves is being sensed and monitored. The sensing of the activity of the glucose-responsive cells is not being monitored for their viability, **and that is never suggested.** Rather, the glucose-responsive cells are being used to provide an *in vivo* monitoring system that indirectly reflects prevailing glucose levels in the patient's tissues and bloodstream. As Palti does not teach what it is asserted to teach and Lemelson fails to teach what it is asserted to teach, the combination of references cannot be found to teach what is asserted in the rejection. The claims cannot be obvious under this ground of rejection based upon these references and what has been asserted as their teachings in the rejection.

In addition, the measurements are made by an invasive procedure with implantation of electrodes (e.g., FIG. 1, FIG. 6A and 6B, FIG. 7, column 8, lines 2-62, etc.) that does not measure cell viability *per se*, but measures glucose levels for purposes of administering insulin levels appropriate for the invasively measured levels of glucose.

**THE REJECTION IS COMPLETELY IN ERROR AND MUST BE
WITHDRAWN**

Independent Basis of Patentability Because of Quantitating of Cell Viability

Additionally, as recited in certain others of these claims (**Claims 54-58**), neither the Lemelson or Palti references disclose how metabolic changes in implanted progenitor or stem cells can be quantitatively measured by non-invasive *in vivo* proton spectroscopy with local or volume RF-coils to obtain quantitative proton observable metabolites such

as GABA, PCr, creatine, choline, and lactate. The quantitative feature of the present application is important because concentrations of lactate above 2-6 millimolar indicate a significant occurrence of dying or dead cells. Thus, unlike Lemelson and Palti, the present application describes how viable cell implants can be distinguished from dead or dying cells based on quantitative regional indications of lactate to metabolite levels.

The present application also discloses how non-invasive imaging technologies can track, in vivo, C-13 labeled glucose introduced directly into brain tissues together with the cell implant. Glucose metabolism in the cell implant is assessed by observing the resulting quantitative data from in vivo conversion of the C-13 labeled glucose into C-13 labeled metabolic by-products. The levels and turnover rates of glucose utilization, as measured by the concentrations of the converted compounds, reflect the ongoing viability of the cell implant. Thus, the methods disclosed by the applicants can be distinguished from the Palti patent in which glucose sensitive cells are implanted into tissue to function as surrogate 'glucodetectors' in patients with insulin-dependent diabetes.

Claims 20-22 have been rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041) in further view of Johnson et al. (US Patent No. 6,051,208)

The sole feature asserted to be added to the teachings of Lemelson in view of Palti is the use of hyperpolarized gas in MRI imaging. Even assuming that the Johnson reference teaches this to be obvious, the teachings of Johnson et al. fails to overcome the fatal deficiencies described above with regard to the combination of Lemelson in view of Palti with respect to claims 5 et seq. This rejection must fail for at least those reasons.

Additionally, the only methodology of Lemelson and Palti is for assessing local sucrose concentration by electrical resistive means. There is no suggestion that or evidence that MRI could be used to determine sucrose concentration. It is not obvious to use MRI methodology taught by Johnson et al. for assessing sucrose intake taught by

Palti. It is furthermore not obvious to attempt to use MRI for an unstated and undirected detection of events not specifically taught by the art of record as indicative of cell viability as claimed in these claims.

Claim 24 has been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041) and further in view of Dinsmore (US Patent No. 6,140,116)

The sole feature asserted to be added to the teachings of Lemelson in view of Palti by Dinsmore is the use of methods to detect at least one of choline, NAA, GABA, phosphocholine and creatine. Even assuming that the Johnson reference teaches this to be obvious, the teachings of Dinsmore fails to overcome the fatal deficiencies described above with regard to the combination of Lemelson in view of Palti with respect to claims 5 et seq. This rejection must fail for at least those reasons.

There is no suggestion that or evidence that any of the systems taught by Lemelson or Palti could be used detect at least one of choline, NAA, GABA, phosphocholine and creatine. It is furthermore not obvious to attempt to use MRI or other systems for an unstated and undirected detection of events not specifically taught by the art of record as indicative of cell viability as claimed in these claims.

All rejections have been traversed and overcome by these arguments.

CONCLUSION

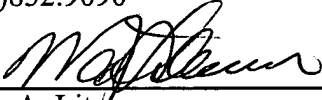
All rejections of record have been shown in detail to be in error. The rejection should be reversed and all claims should be indicated as allowable.

Applicants believe the claims are in condition for allowance and request reconsideration of the application and allowance of the claims. The Examiner is invited to telephone the below-signed attorney at 952-832-9090 to discuss any questions that may remain with respect to the present application.

Respectfully submitted,
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By their Representatives,
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Date 27 JANUARY 2006 By



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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Box: APPEAL BRIEF - PATENTS, P.O. BOX 1450; Commissioner for Patents, Alexandria, VA 22313-1450 on JANUARY __27__, 2006.

Name: Mark A. Litman



Signature

CLAIMS APPENDIX

1. (CANCELLED)

2. (CANCELLED)

3. (CANCELLED)

4. (CANCELLED)

5. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.

6. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region, wherein said non-destructively observing comprises magnetic resonance imaging and wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.

7. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said property is monitored by observation of at least one parameter selected from the group consisting of local lactate levels, local glucose turnover, local phosphorous high-energy metabolite concentrations, local F-19 labeled metabolites, alterations in tissue sodium, and changes in the conversion rates of O₂ gas to H₂O water.

8. CANCELLED

9. (PREVIOUSLY PRESENTED) The method of claim 6 wherein said property is

monitored by observation of at least one parameter selected from the group consisting of local lactate levels, local glucose turnover, local phosphorous high-energy metabolite concentrations, local F-19 labeled metabolites, alterations in tissue sodium, and changes in the conversion rates of O₂ gas to H₂O water.

10. CANCELLED

11. (PREVIOUSLY PRESENTED) The method of claim 5 wherein said property is monitored by at least one technique selected from the group consisting of proton spectroscopy, monitoring of C-13 labeled glucose, monitoring by P-31 MR spectroscopy, monitoring of local F-19 labeled metabolites, monitoring of Na-23 levels, and monitoring of ¹⁷O₂ gas conversion to H₂¹⁷O water.

12. (ORIGINAL) The method of claim 6 wherein said property is monitored by at least one technique selected from the group consisting of proton spectroscopy, monitoring of C-13 labeled glucose, monitoring by P-31 MR spectroscopy, monitoring of local F-19 labeled metabolites, monitoring of Na-23 levels, and monitoring of ¹⁷O₂ gas conversion to H₂¹⁷O water.

13. (PREVIOUSLY PRESENTED) The method of claim 5 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue and a local multi-tuned MRI RF coil.

14. (PREVIOUSLY PRESENTED) The method of claim 6 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue and a local multi-tuned MRI RF coil.

15. (ORIGINAL) The method of claim 9 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue and a local multi-tuned MRI RF coil.

16. (ORIGINAL) The method of claim 12 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue and a local multi-tuned MRI RF coil.

17. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said property comprises blood flow or changes in blood flow as vascular supply is developed.

18. (PREVIOUSLY PRESENTED) The method of claim 17 wherein said non-destructively observing comprises magnetic resonance imaging and said property comprises blood flow or changes in blood flow as vascular supply is developed.

19. (PREVIOUSLY PRESENTED) The method of claim 17 wherein said property is monitored by observation of at least one parameter selected from the group consisting of local lactate levels, local glucose turnover, local phosphorous high-energy metabolite concentrations, local F-19 labeled metabolites, alterations in tissue sodium, and changes

in the conversion rates of O₂ gas to H₂O water said property comprises blood flow or changes in blood flow as vascular supply is developed.

20. (ORIGINAL) The method of claim 17 wherein blood flow or changes in blood flow are measured by observation of at least one material selected from the group consisting of labeled H₂O water, contrast-agent infusion of T1-shortening agents or T2*-shortening agents, local introduction of hyperpolarized Xenon gas, or optically-active coloring agents.

21. (ORIGINAL) The method of claim 18 wherein blood flow or changes in blood flow are measured by observation of at least one material selected from the group consisting of labeled H₂O water, contrast-agent infusion of T1-shortening agents or T2*-shortening agents, local introduction of hyperpolarized Xenon gas, or optically-active coloring agents.

22. (ORIGINAL) The method of claim 19 wherein blood flow or changes in blood flow are measured by observation of at least one material selected from the group consisting of labeled H₂O water, contrast-agent infusion of T1-shortening agents or T2*-shortening agents, local introduction of hyperpolarized Xenon gas, or optically-active coloring agents.

23. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability

or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said non-destructively observing comprises magnetic resonance imaging and said property comprises anisotropic water diffusion.

24. (PREVIOUSLY PRESENTED) The method of claim 5 wherein said property comprises the local concentrations of at least one of choline, NAA, GABA, phosphocholine, and creatine.

25. (PREVIOUSLY PRESENTED) The method of claim 6 wherein the property is selected from the group consisting of a) local tissue density and cell populations, b) local electrical activity, c) local oxygenated/deoxygenated hemoglobin and changes in the local T2* reflecting the alterations in tissue oxygenation, d) changes in the vascular reserve and response to oxygenation stresses, e) tissue fluorescence and bioluminescence, f) tissue fluorescence and bioluminescence, g) electrical impedance, and h) local tissue temperature.

26. (ORIGINAL) The method of claim 1 wherein the property is selected from the group consisting of a) local tissue density and cell populations, b) local electrical activity, c) local oxygenated/deoxygenated hemoglobin and changes in the local T2* reflecting the alterations in tissue oxygenation, d) changes in the vascular reserve and response to oxygenation stresses, e) tissue fluorescence and bioluminescence, f) tissue fluorescence and bioluminescence, g) electrical impedance, and h) local tissue temperature.

27. (CANCELLED)

28. (CANCELLED)

29. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, said method being performed with a medical device that supports at least one sensing function comprising:

- non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture have been transplanted;
- sensing a property within said region of a patient that is indicative of cell metabolism;
- repeating or continuing said sensing of a property over a period of time in which said property changes; and

using data from sensing changes in said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region, wherein said data from sensing changes in said property indicates active metabolic function in transplanted cells, and wherein changes in said property are monitored by at least one technique selected from the group consisting of proton spectroscopy, monitoring of C-13 labeled glucose, monitoring by P-31 MR spectroscopy, monitoring of local F-19 labeled metabolites, monitoring of Na-23 levels, and monitoring of 17O_2 gas conversion to H_2^{17}O water.

30. (CANCELLED)

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52. (CANCELLED)

53. (CANCELLED)

54. (PREVIOUSLY PRESENTED) The method of claim 5 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

55. (PREVIOUSLY PRESENTED) The method of claim 6 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

56. (PREVIOUSLY PRESENTED) The method of claim 7 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

57. (PREVIOUSLY PRESENTED) The method of claim 17 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

58. (PREVIOUSLY PRESENTED) The method of claim 19 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

59. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells, the method being performed with a medical device that supports at least one sensing function, the method comprising:

- non-destructively observing a region of a patient to where progenitor or stem cells have been transplanted;

- sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells; and

- using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells within the region wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and

BRIEF ON APPEAL

Serial Number: 09/606,137

Filing Date: June 28, 2000

Title: IMAGING METHOD FOR VISUALIZING IMPLANTED LIVING CELLS

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Docket No.: 500.003US1

volumetric decrease of cell population.

EVIDENCE APPENDIX

No declarative of affidavit evidence or comparisons were submitted under 37 CFR 1.132.

RELATED PROCEEDINGS APPENDIX

Applicants and the attorney of record state that there are no related proceedings in any court system in the United States or elsewhere throughout the world relating to this application. There are no quasi-judicial occurrences relating to the subject matter of this Application in the US PTO, State Courts or the US court system relating to the subject matter of this application.